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STATE-OF-THE-ART PAPERS

Anti-Inflammatory Strategies for Ventricular Remodeling Following ST-Segment Elevation Acute Myocardial Infarction

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Acute myocardial infarction (AMI) leads to molecular, structural, geometric, and functional changes in the heart in a process known as ventricular remodeling. An intense organized inflammatory response is triggered after myocardial ischemia and necrosis and involves all components of the innate immunity, affecting both cardiomyocytes and noncardiomyocyte cells. Inflammation is triggered by tissue injury; it mediates wound healing and scar formation and affects ventricular remodeling. Many therapeutic attempts aimed at reducing inflammation in AMI during the past 3 decades presented issues of impaired healing or increased risk of cardiac rupture or failed to show any additional benefit in addition to standard therapies. More recent strategies aimed at selectively blocking one of the key factors upstream rather than globally suppressing the response downstream have shown some promising results in pilot trials. We herein review the pathophysiological mechanisms of inflammation and ventricular remodeling after AMI and the results of clinical trials with anti-inflammatory strategies. (J Am Coll Cardiol 2014;63:1593–603) © 2014 by the American College of Cardiology Foundation

Acute myocardial infarction (AMI) remains a leading cause of death worldwide (1). Despite reperfusion strategies, patients with large AMI who survive the initial ischemic event are at higher risk of the development of HF in a process referred as ventricular remodeling (2). The term ventricular remodeling, first used by Pfeffer et al. (3) in 1985, refers to changes in ventricular geometry (dilation, sphericity, wall thinning) and stiffness, as well as epigenetic, molecular, and functional changes that include both cardiomyocytes and other cells of the heart, in the infarct area, and in the remote viable myocardium (4). Ventricular remodeling is a powerful prognostic factor after AMI (5) and has been identified as a target for intervention.

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Despite modern reperfusion strategies (with a goal of door-to-balloon time of <90 min) and neurohormonal blockade therapies (inhibitors of the renin-angiotensin-aldosterone system and of the adrenergic system), the incidence of HF after ST-segment elevation AMI remains unacceptably high, and there is an urgent need for novel treatments to improve post-AMI quality of life and survival. This suggests that the current therapeutic paradigm still misses one or more key pathophysiological mechanisms.

Parallel to the interest in reperfusion and neurohormonal blockade, much interest has been devoted to understanding the role of inflammation in AMI (6), leading to a large volume of experimental preclinical data and clinical observation evidence but, unfortunately, not to any clinically effective anti-inflammatory treatments for AMI.

The aim of this review is to discuss the activation of the inflammatory response and its role in post-AMI ventricular remodeling, the basis of preclinical research, the potential reasons for failure to translate, and future perspectives in the field.

Pathophysiology

The heart has limited anaerobic metabolism and depends on oxygen. During AMI, the oxygen supply is reduced and adenosine triphosphate is no longer produced, with

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Abbreviations and Acronyms

AAT = alpha$_1$-trypsin
AMI = acute myocardial infarction
COX = cyclooxygenase
CRP = C-reactive protein
CVF = cobra venom factor
HF = heart failure
IL = interleukin
IL-1R1 = interleukin 1 receptor 1
IVIG = intravenous immunoglobulin
MACE = major adverse cardiac event(s)
MMP = metalloproteinase
PCI = percutaneous coronary intervention
PI3K = phosphoinositide 3-kinase
RCT = randomized clinical trial
STEMI = ST-segment elevation myocardial infarction
TNF = tumor necrosis factor
TNFR = tumor necrosis factor receptor

impairment of the sodium-potassium (Na^+-K^+ ATPase) pump and loss in membrane integrity, leading to death (6,7).

After the initial ischemic event, an intense inflammatory response is observed, mainly characterized by infiltration with neutrophils, followed by monocytes/macrophages and lymphocytes. Infiltrating monocytes first express a proinflammatory (M1) phenotype, followed by a switch to an angiogenic and fibrotic phenotype (M2) (8,9). Infiltrating lymphocytes, although smaller in number, also play a key role in remodeling. CD4 T-helper lymphocytes shift to a Th1 phenotype, whereas regulatory T cells are necessary for resolution of inflammation (6,10). In the initial few days, the infarct starts to expand as a result of the loss of passive tension. Infarct expansion is characterized by acute ventricular dilation, infarct wall thinning (without additional necrosis), and cardiomyocyte stretching. Extracellular matrix degradation promotes cardiomyocyte slippage and scar thinning. Cardiac fibroblasts generate a noncompliant collagen scar to maintain the ventricular geometry and prevent aneurysm formation. This process is followed by maturation of the scar. Apoptosis of infiltrating neutrophils and a phenotypic switch in macrophages and lymphocytes are involved in the resolution of the inflammatory process (6,8,10).

This healing process in post-AMI ventricular remodeling can be divided into 3 partially overlapping phases (6): 1. the inflammatory phase; 2. the proliferative phase; and 3. the maturation phase. The inflammatory phase is mediated by cytokines leading to recruitment of leukocytes. Cell debris activates the inflammasome, a macromolecular structure that activates caspase-1 and the conversion of pro-interleukin (IL)-1β to mature IL-1β (11,12). The formation and activation of the inflammasome amplify tissue injury and the local and systemic inflammatory response (11,12). Leukocytes remove necrotic cells while releasing cytokines and growth factors. Neutrophils eventually undergo apoptosis, leading to a gradual disappearance of the infiltrate. In the proliferative phase, fibroblasts proliferate and synthesize collagen to form a scar.

The most effective therapeutic intervention to reduce myocardial injury is timely and effective myocardial reperfusion. The process of myocardial reperfusion, however, can itself induce further cardiomyocyte death with a phenomenon known as myocardial reperfusion injury (13).

Over time, the increased wall stress and neurohormonal activation, however, causes apoptosis of the cardiomyocytes in the nonischemic area leading to left ventricular wall thinning and chamber dilation, producing a spherical geometry with an increased left ventricular mass but decreased relative wall thickness (eccentric hypertrophy) (7). Although ventricular dilation observed during the initial phases may be beneficial in maintaining cardiac output via an increase in ventricular filling volume, these compensatory mechanisms become detrimental when sustained over time, leading to cardiac dysfunction and heart failure (Fig. 1).

Anti-Inflammatory Treatments

Several experimental studies in animals have explored treatments aimed at modulating inflammation during AMI. Only those strategies that were eventually tested in clinical studies are discussed in detail in this review.

Glucocorticoids. Glucocorticoids are potent anti-inflammatory agents that act via 3 mechanisms (14): first, binding a receptor in the cytosol that moves to the nucleus and binds as a dimer to DNA sequences called glucocorticoid-responsive elements, modifying DNA transcription; second, the cortisol-glucocorticoid receptor complex inhibits nuclear factor κB, regulating the transcription of proinflammatory mediators; and third, via membrane-associated receptors (nongenomic pathways) independent of gene expression, such as activation of endothelial nitric oxide synthase.

In experimental animal models, treatment with glucocorticoids showed conflicting results (15,16), associated with impaired healing, scar thinning, ventricular aneurysm, and increased risk of ventricular rupture (17,18). Several rather small clinical studies tested the effects of glucocorticoids in patients with AMI, showing conflicting results. A recent systematic review and meta-analysis (16 studies, n = 4,000) in AMI included registries, case-control studies, and nonrandomized and randomized clinical trials (RCTs) (19). The analysis of mortality (11 studies, n = 2,646) showed a 26% relative risk reduction with glucocorticoid therapy and no excess risk of rupture. However, there was no significant survival benefit when only RCTs or larger studies (n = >100) were included. Differences in study design, investigational agents (e.g., hydrocortisone, dexamethasone, prednisone, methylprednisone), and dosing regimens make it difficult to draw any definitive conclusions. Finally, none of the studies used a percutaneous coronary intervention (PCI) as a reperfusion strategy, and some studies were performed with no reperfusion strategy used. Overall, treatment with glucocorticoids was not harmful in this group and in some instances might be even beneficial. The impairment in infarct healing with corticosteroids is not supported by clinical trials, and it is either only seen in some subsets of patients (i.e., long-term steroid use, first AMI, transmural AMI without reperfusion)

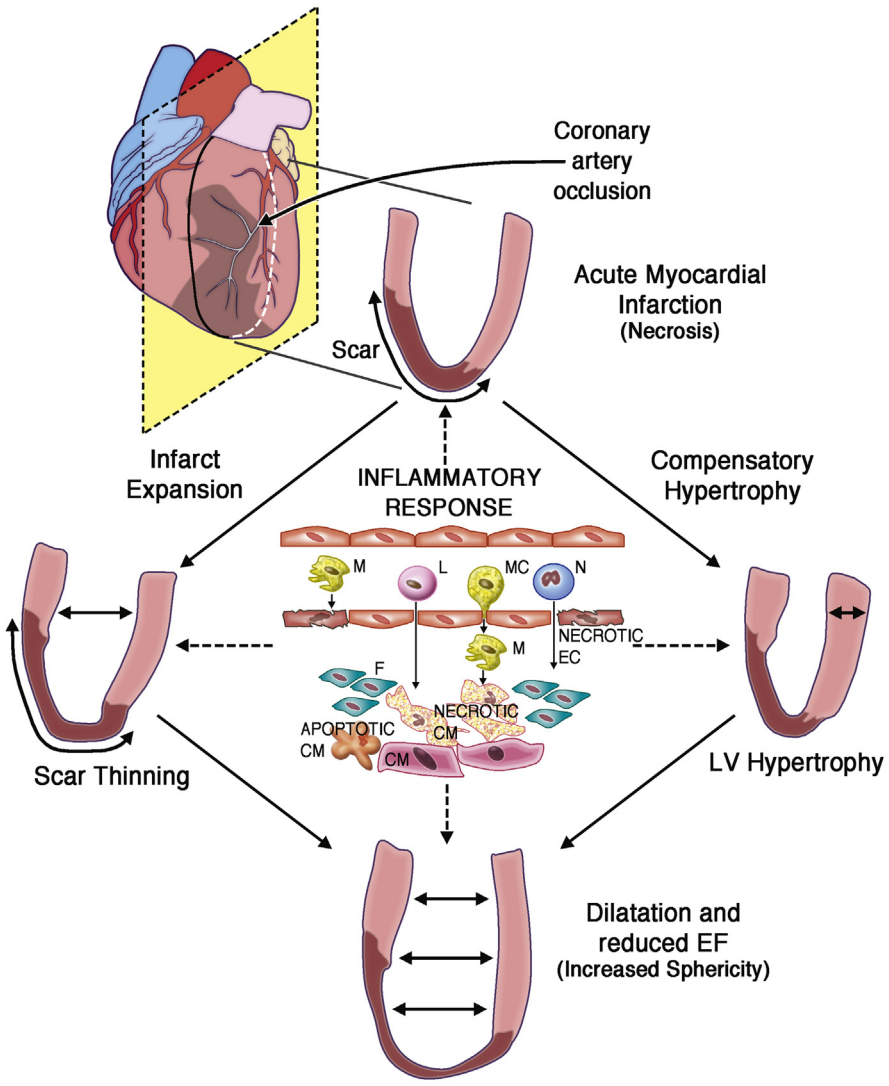

Figure 1 **Pathophysiology of Ventricular Remodeling After Acute Myocardial Infarction**

After coronary artery occlusion, ischemia ensues, cardiomyocytes die, and healing and scar formation begin **(top)**. The remodeling process can lead to left ventricular (LV) dilation, initially with preservation of ejection fraction (EF) at first (Frank-Starling mechanism), but infarct expansion with scar thinning may occur **(left)**, or compensatory hypertrophy of the noninfarcted area may be sufficient to limit, at least initially, ventricular dilation **(right)**. If the stimuli for adverse remodeling process persist over time, ventricular dilation and wall thinning lead to reduced ejection fraction (EF) and heart failure **(bottom)**. Inflammation plays a critical role in ventricular remodeling **(center)**. Leukocytes (macrophages [M], lymphocytes [L], monocytes [MC], neutrophils [N]) leave the bloodstream via endothelial cells (EC) and clear necrotic cardiomyocytes (CM), whereas fibroblasts (F) produce a collagen-based scar. LV = left ventricular.

or is more of a perceived rather than a real effect. However, considering the uncertain benefit and the adverse effects of volume retention, edema, hyperglycemia, and muscular atrophy, the use of glucocorticoid in AMI is currently not advised. Accordingly, current clinical guidelines for ST-segment elevation myocardial infarction (STEMI) recommend against glucocorticoid treatment (20,21).

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also broad anti-inflammatory drugs that inhibit prostanoid production from arachidonic acid through inhibition of cyclooxygenase (COX) (22). Two isoforms of COX exist: COX-1 is constitutively expressed in most cell types and is the only COX isoform in platelets, whereas COX-2 expression is mainly induced during inflammation.

Experimental studies with NSAIDs showed conflicting results (23–27); they seem to delay rather than decrease ischemic necrosis (28), with the risk of allowing ventricular wall tension to act on deformable myocardium for a longer time leading to aneurysm formation and rupture (29).

Observational clinical studies showed an association between NSAID use, worse clinical outcome (30), and ventricular rupture after AMI (31). An experimental study in

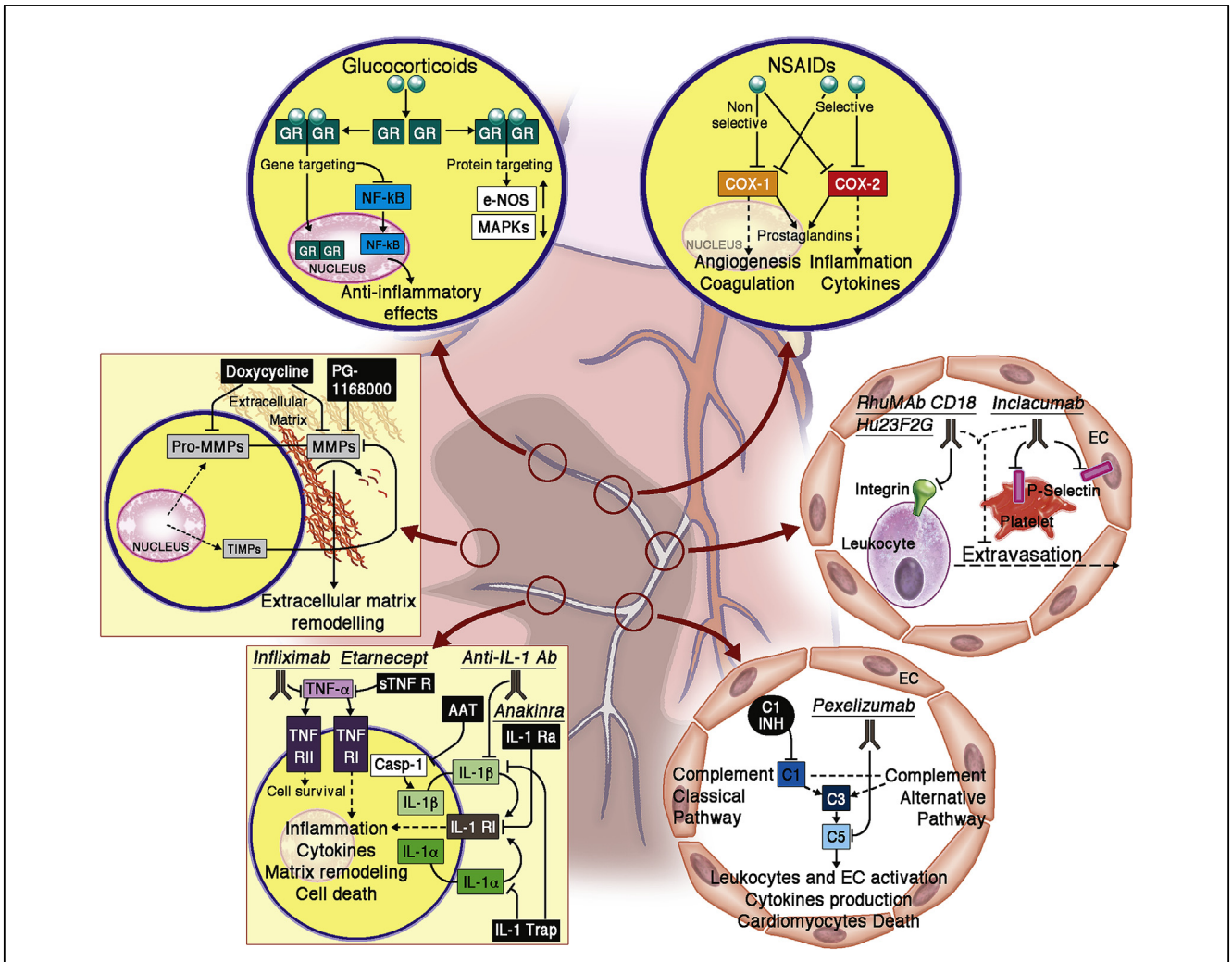

Figure 2 **Anti Inflammatory Targets in Cardiac Remodeling After Acute Myocardial Infarction**

Mechanisms of action for the different anti-inflammatory treatments. **(Upper left)** Glucocorticoids bind a receptor (GR) in the cytosol that homodimerizes and translocates to the nucleus to exert anti-inflammatory effects, whereas other nongenomic effects are related to endothelial nitric oxide synthase (e-NOS) stimulation and mitogen-activated protein kinases (MAPKs). NF-kB = nuclear factor κB. **(Upper right)** Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase enzyme (COX) either selectively (COX 1 or 2) or non-selectively. **(Left)** Matrix metalloproteinases (MMPs) are endoproteinases that degrade the extracellular matrix participating in migration of inflammatory cells. TIMPs = Tissue inhibitors of metalloproteinases. **(Right)** Integrins are leukocyte cell adhesion molecules, essential for infiltrating the myocardium through the endothelium. P-selectin is also expressed in activated platelets. EC = endothelial cell. **(Bottom left)** Tumor necrosis factor (TNF)-α is cytokine with pleiotrophic effects; whereas signaling through the TNF-α receptor I (TNFRI) is proinflammatory, signaling through the TNFRII is beneficial. Etarnecept is a recombinant soluble TNFR (sTNFR). Interleukin (IL)-1β is activated from pro-IL-1β through caspase-1 (Casp-1), and alpha$_1$-antitrypsin (AAT) inhibits Casp-1. IL-1 binds the IL-1 receptor (IL-1R) as well as the IL-1R antagonist (IL-1Ra). Anakinra is a recombinant IL-1Ra, whereas IL-1Trap is a soluble IL-1R. Ab = antibody. **(Bottom right)** The classic pathway of the complement cascade starts with C1 activation. A soluble C1 receptor (sC1R) or direct C1 inhibitors inhibit this pathway. C5 is downstream activated, leading to inflammation and cardiomyocyte injury. C1INH = C1 esterase inhibitor.

patients with AMI and symptomatic pericarditis showed that treatment with either ibuprofen or indomethacin led to infarct expansion (32). Although the majority of these studies are dated and involved patients with nonreperfused AMI who are at greatest risk of infarct expansion, NSAIDs also led to a significant increase in blood pressure values, reduced renal blood flow, increased platelet aggregation, and increased risk of gastrointestinal bleeding. Therefore, current clinical guidelines recommend against NSAID treatment, and discontinuation at the time of STEMI is indicated (20,21). Moreover, long-term NSAID use is associated with an increased risk of incident and recurrent AMI (33,34).

Selective COX-2 inhibitors also showed conflicting results in experimental studies in AMI (35–39). In the NUT-2 (Nonsteroidal Anti-Inflammatory Drugs in Unstable Angina Treatment-2) pilot study (n = 120) meloxicam, a preferential COX-2 inhibitor, showed a decreased composite endpoint of recurrent angina, AMI, and death when treatment was given for 30 days (40). COX-2 inhibitors, however, have effects on blood pressure and renal blood flow similar to those of NSAIDs, and therefore

current guidelines advise against their use in patients with AMI.

Integrins. Activated neutrophils play a key role in reperfusion injury (41). Neutrophils infiltrate the ischemic myocardium through endothelial adhesion molecules, which lead to the development of antibodies against these adhesion molecules (CD18, CD11) with promising results in experimental AMI in mice (42), rabbits (43), dogs (44–46), and primates (47) (Fig. 2).

The LIMIT-AMI (Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction) trial (48) in STEMI (394 patients with fibrinolysis) showed that treatment with a humanized monoclonal antibody against CD18 (rhuMAb CD18) failed to improve coronary reperfusion on angiography, ST-segment resolution, or infarct size at 5 days, with a nonsignificant trend toward increased infections and bleeding complications. The HALT-AMI trial (49) also failed to show any beneficial effect in STEMI (420 patients with primary PCI) treated with a recombinant antibody against CD11/CD18 (Hu23F2G). Although infections were also significantly increased with Hu23F2G, a trend toward a decreased incidence of death, reinfarction, and HF at 30 days was observed. A possible explanation for negative results observed with these agents is that the duration of ischemia observed in trials is longer than that in experimental models of ischemia-reperfusion, leading to irreversible endothelial cell barrier damage and thus limiting the efficacy of the proposed intervention.

P-selectin is another adhesion molecule expressed on activated endothelial cells and platelets and is essential for leukocyte tethering and rolling in the vessel wall to infiltrate the myocardium, similar to CD18/11b (50). In addition, P-selectin is highly expressed in activated but not resting platelets. In experimental reperfused AMI, a soluble P-selectin glycoprotein ligand-immunoglobulin was shown to decrease infarct size and inflammation (51). A phase II trial (SELECT-ACS [Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST Elevation Myocardial Infarction] trial) in 322 patients with non-STEMI showed that treatment with a monoclonal antibody against P-selectin (inclacumab) appears to reduce myocardial damage as measured by creatine phosphokinase and troponin release (52). Nevertheless, the clinical event rates trended in the opposite direction, with a trend toward more unfavorable events in treated versus untreated patients (53). Moreover, the effects of these drugs on long-term ventricular remodeling were not assessed, and no study has follow-up longer than 30 days, making it difficult to translate the results to clinical practice. Clinical studies targeting integrins are summarized in Table 1.

Complement cascade. Complement cascade is activated early during AMI and actively participates in ischemia-reperfusion injury via various mechanisms: activating leukocytes and endothelial cells, increasing proinflammatory cytokine release, and causing cardiomyocyte cell death (6,41). Complement cascade is activated via a classic and alternative pathway, whereas complement cell death is mediated by the membrane attack complex (Fig. 2) (54).

Blockade of the classic pathway of complement activation by a C1 esterase inhibitor was beneficial in experimental models of ischemia-reperfusion in cats (55), rats (56–58), pigs (59), and rabbits (60). However, higher doses of C1 esterase inhibitor showed no protective effects and may even promote coagulation and inhibit thrombolysis (61).

In a safety clinical study, treatment with a C1 inhibitor was well tolerated, and no drug-related adverse effects were observed in 22 patients with STEMI reperfused with fibrinolysis (62). Of note, the drug was given at least 1 to 2.5 h after termination of fibrinolytics to avoid plasmin inhibition as a prothrombotic effect.

Complement depletion with cobra venom factor (CVF) reduces infarct size in dogs after ischemia-reperfusion (63). The immunogenicity of CVF led to the development of

Table 1 Clinical Studies With Pharmacological Strategies Against Integrins

Study, Year (Ref. #)	Population (N)	Reperfusion Strategy	Treatment	Primary Endpoint (Follow-Up)	Results	Observations
LIMIT-AMI, 2001 (48)	STEMI <12 h (394)	rtPA	MAb for CD18 (rhuMAb CD18) in 2 doses	CTFC on angiography (90 min)	CTFC: Placebo 46 ± 13 vs. 51 ± 32 and 45 ± 29 rhuMAb CD18 (low and high dose, respectively) (p = NS)	No difference in secondary outcomes (infarct and ST-segment resolution)
HALT-AMI, 2002 (49)	STEMI <6 h (420)	PCI	Recombinant Ab for CD11/CD18 (Hu23F2G) in 2 doses	Infarct size (SPECT) at 5 to 9 days	Placebo 16% vs. 17.2% and 16.6% Hu23F2G (low and high dose, respectively) (p = 0.8)	No difference in clinical events at 1 month
SELECT-ACS, 2013 (52)	NSTEMI (544)	PCI	MAb for P-selectin (inclacumab) in 2 doses	Change in troponin I (baseline vs. 16 and 24 h)	16 h: placebo 77% vs. 38% inclacumab high dose (RRR: 22%, p = 0.07) 24 h: placebo 58% vs. 19% inclacumab high dose (RRR: 24%, p = 0.05)	No effect for the low dose. Trend toward more clinical events with treatment

Ab = antibody; CTFC = corrected Thrombolysis In Myocardial Infarction frame count; MAb = monoclonal antibody; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RRR = relative risk reduction; rtPA = recombinant tissue plasminogen activator; rhuMAb = humanized monoclonal antibody; STEMI = ST-segment elevation myocardial infarction.

humanized CVF that also decreased myocardial ischemia-reperfusion injury in mice (64).

C5 is activated both in the classic and alternative pathways and is a key member of the membrane attack complex. C5a is the most potent anaphylatoxin that attracts and stimulates neutrophils, causing their sequestration within capillaries (54). Inhibition of C5 activation using monoclonal antibodies was shown to reduce infarct size in rats with ischemia-reperfusion through reduction in neutrophil infiltration and cardiomyocyte apoptosis (65).

Pexelizumab is a humanized antibody against C5 that was tested in different scenarios of AMI, unfortunately without the expected beneficial effect. The COMPLY (COMPlement inhibition in myocardial infarction treated with thromboLYtics) trial (66) (943 patients with fibrinolysis) failed to reduce infarct size or reduce major adverse cardiac adverse events (MACE) in patients with STEMI. The phase II COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) trial (67), tested the effects of pexelizumab in a similar group of patients (STEMI within 6 h, 960 patients) but undergoing primary PCI. Although no differences in infarct size measured with creatine phosphokinase area under curve were observed, treatment with pexelizumab showed a significant decrease in mortality at 90 days (1.8% vs. 5.9% for placebo, $p = 0.014$). Therefore, the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial (68), a phase III RCT (5,754 patients with primary PCI) was completed to confirm and expand the results of the COMMA trial. Unfortunately, pexelizumab showed no effect on the primary endpoint of mortality at 30 days or MACE at 3 months. Clinical studies targeting the complement are summarized in Table 2.

Cytokines. Leukocytes are mobilized to the site of injury by cytokines and chemokines. IL-1 is the prototypical proinflammatory cytokine (69). Two forms of IL-1 exist, IL-1α and IL-1β. Both forms are synthesized as precursors; pro-IL-1α is, however, already active and has also a role as nuclear transcription factor, whereas pro-IL-1β is inactive until cleaved by caspase-1 in the inflammasome to become active IL-1β. Both IL-1α and IL-1β bind the same IL-1 receptor 1 (IL-1R1) membrane signaling receptor. IL-1β is considered the predominant circulating form of IL-1. IL-1 binds a signaling membrane receptor (IL-1R1) associated with an accessory protein (IL-1 accessory protein) that binds the myeloid differentiation factor 88. This messenger activates IL-1 receptor–associated kinase type 4 releasing nuclear factor κB, which transports to the nucleus to synthesize most proinflammatory cytokines and amplify the inflammatory response. A type 2 receptor transduces no signal. IL-1 receptor antagonist is a third member of IL-1 family that binds to the IL-1R1 without eliciting any downstream signaling (70). Experimental studies showed that the IL-1 family is upregulated in AMI (71,72), leading to ventricular dysfunction (12,73–75) and inflammation (70). In pre-clinical models of experimental AMI in mice, IL-1 blockade either with the human recombinant IL-1 receptor agonist (anakinra) (76), a soluble receptor acting as a trap for circulating IL-1β and IL-1α (77), antibodies against IL-1β (78,79), downstream myeloid differentiation factor 88 (80) inhibition, or genetic blockade (81), all improved ventricular remodeling and cardiac function after AMI without impairing infarct healing or scar formation (12) (Fig. 2).

The encouraging results of IL-1 blockade in pre-clinical models, led to 2 pilot clinical trials with anakinra: the VCU-ART (Virginia Commonwealth University Acute Remodeling Trial) (82) and VCU-ART2 (83). These phase II pilot studies enrolled 40 patients with reperfused STEMI with primary PCI randomized to daily treatment with anakinra or placebo for 14 days. Anakinra was well tolerated and associated with a favorable effect on C-reactive protein (CRP) levels and trends toward more favorable left ventricular remodeling and a reduced incidence of HF at 3 months (30% vs. 5%). Of note, the incidence of HF was 30% at 3 months in this placebo cohort of patients despite nearly normal ventricular dimensions and function, which suggests that with current reperfusion and therapeutic strategies, HF after STEMI may occur also with slight or undetectable ventricular remodeling. A third pilot study

Table 2 Clinical Studies With Pharmacological Strategies Against the Complement Cascade

Study, Year (Ref. #)	Population (N)	Reperfusion Strategy	Treatment	Primary Endpoint (Follow-Up)	Results	Observations
De Zwaan, 2002 (62)	STEMI (22)	STK or rtPA	C1 inhibitor (Cetor) in 3 doses	Safety (48 h)	Cetor was well tolerated and inhibited C4 fragments	Cetor reduces AUC for CK-MB 57%, $p = 0.001$
COMPLY, 2003 (66)	STEMI <6 h (943)	STK, rtPA and other fibrinolytics	MAb for C5 (pexelizumab) bolus ± infusion	Infarct size by CK-MB AUC (72 h)	CK-MB AUC (ng/ml): placebo 5,230 vs. 4,952 (bolus) and 5,557 (with infusion) Pexelizumab (p = NS)	No difference in clinical events at 3 months
COMMA, 2003 (67)	STEMI <6 h (960)	PCI	MAb for C5 (pexelizumab) bolus ± infusion	Infarct size by CK-MB AUC (72 h)	CK-MB AUC (ng/ml): placebo 4,393 vs. 4,526 (bolus) and 4,713 (with infusion) Pexelizumab (p = NS)	Pexelizumab (bolus + infusion) reduced 90-day mortality (RR: 0.3, 95% CI: 0.46–1.29, $p = 0.014$)
APEX-AMI, 2007 (68)	STEMI <6 h (2,885)	PCI	MAb for C5 (pexelizumab) bolus + infusion	All-cause mortality (30 days)	No difference: placebo 4.1% vs. pexelizumab 3.9%, $p = 0.78$	No difference in other clinical endpoints

AUC = area under curve; CI = confidence interval; CK-MB = creatine kinase-myocardial band; RR = relative risk; STK = streptokinase; other abbreviations as in Table 1.

Table 3 Clinical Studies With Pharmacological Strategies Against Cytokines

Study, Year (Ref. #)	Population (N)	Reperfusion Strategy	Treatment	Primary Endpoint (Follow-Up)	Results	Observations
VCU-ART, 2010 (82)	STEMI (10)	PCI	Anakinra (IL-1Ra) for 14 days	Ventricular remodeling as ΔLVESVI on cardiac MRI (3 months)	Placebo: +2 ml/m^2 vs. anakinra: −3.2 ml/m^2 ($p = 0.033$)	ΔCRP correlated with remodeling ($r^2 = 0.71$, $p = 0.02$); more events in the placebo group
VCU-ART2, 2013 (83)	STEMI (30)	PCI	Anakinra (IL-1Ra) for 14 days	Ventricular remodeling as ΔLVESVI on cardiac MRI (3 months)	Placebo: +1.0 ml/m^2 vs. anakinra: +1.4 ml/m^2 ($p = 0.8$)	VCU-ART and VCU-ART2 combined events showed reduction in HF with anakirna (30% vs. 5%, $p = 0.035$)
Padfield GJ et al, 2013 (108)	NSTEMI at day 3 (26)	NS	Etarnecept (TNF-α blocker)	Leukocytes, cytokines, platelet activation, endothelial dysfunction and fibrinolysis (24 h)	Reduced neutrophil count and IL-6 but increased platelet-monocyte aggregation	No effect on endothelial and fibrinolytic functions

ΔCRP = change in C-reactive protein level; HF = heart failure; HR = hazard ratio; IL = interleukin; IL-1Ra = interleukin-1 receptor antagonist; LVEF = left ventricular ejection fraction; ΔLVESVI = change in left ventricular end-systolic volume index; LVESVI = left ventricle end-systolic volume index; MRI = magnetic resonance imaging; NYHA = New York Heart Association; TNF = tumor necrosis factor; NS = not specified; other abbreviations as in Table 1.

(VCU-ART3) is being planned that will test 2 different doses of anakinra in patients with STEMI who are at increased risk of HF (84).

Alpha$_1$-antitrypsin (AAT) is an abundant serine protease inhibitor, up-regulated in AMI as an acute phase reactant (85). AAT also exerts anti-inflammatory effects independent of the serine protease-inhibiting activity, including inhibition of caspase-1 (86) (Fig. 2). Experimental studies showed that AAT improved ventricular remodeling after reperfused AMI in mice (86). A phase II pilot trial will test the safety and efficacy of AAT in patients with STEMI (87).

IL-6 is a key secondary cytokine produced by inflammatory cells in response to various stimuli including IL-1 (88,89). IL-6 first binds to the IL-6 receptor (CD126), and the subsequent complex associates with the receptor subunit glycoprotein 130 (CD130) (89). Experimental studies provided conflicting and inconclusive results regarding the role IL-6 in ventricular remodeling (90,91). Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor (92), currently being tested in an RCT in patients with non-STEMI (93).

IL-10, in contrast, is an anti-inflammatory cytokine. Experimental studies showed conflicting results with some showing protective and some showing detrimental effects of IL-10 (94,95). To date, no clinical study in patients with AMI has been performed.

CRP is synthesized and released from hepatocytes in response to cytokines, primarily IL-6. Experimental studies have shown that CRP can promote inflammation and apoptosis in the mouse heart, and overexpression exacerbates ventricular remodeling after AMI (96), whereas specific CRP removal by apheresis reduced infarct size in reperfused AMI in pigs (97). There have been no clinical studies aimed at inhibiting or removing CRP in patients with AMI to date.

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine released by inflammatory cells early in AMI (98,99). TNF-α binds 2 types of receptors: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). TNFR1 recruits TNFR1-associated death domain protein leading to cardiomyocyte death, whereas TNFR2 preferentially activates cell survival pathways (100). TNF-α is up-regulated early in AMI, promoting cardiac dysfunction (101), inflammation (6), and cardiomyocyte apoptosis (102). Blockade of the TNF-α system in experimental AMI, however, led to conflicting results (103–105): TNFR1 mediates detrimental effects of TNF-α after AMI, whereas data on the role of TNFR2 in AMI are controversial (106,107). A small recent clinical trial with etanercept, a TNF-α blocker acting as a circulating trap, in 26 patients with AMI showed reduced neutrophil count and plasma IL-6 concentrations at 24 h but unexpectedly increased platelet-monocyte aggregation (108). No other clinical trials to date have tested the effects of TNF-α blockade in STEMI. However, disappointing results observed with TNF-α blockers (etanercept and

Table 4 Clinical Studies With Pharmacological Strategies Against Metalloproteinases

Study, Year (Ref. #)	Population (N)	Reperfusion Strategy	Treatment	Primary Endpoint (Follow-Up)	Results
PREMIER, 2006 (113)	STEMI + LVEF 15%–40% (203)	Any or none (90% PCI)	PG-116800 (MMP inhibitor) from day 2	Ventricular remodeling as ΔLVESVI on echocardiography (3 months)	Placebo: +5.5 ml/m^2 vs. PG-116800: +5.1 ml/m^2 ($p = 0.42$)
TIPTOP, 2013 (115)	STEMI <12 h + LVEF <40% (120)	PCI	Doxycycline (100 mg twice daily) for 14 days	Ventricular remodeling as ΔLVESVI on echocardiography (6 months)	Placebo: +13.4% vs. doxycycline +0.4% ($p = 0.012$)

MMP = metalloproteinase; other abbreviations as in Tables 1 and 3.

infliximab) in patients with HF, with a dose-dependent increase in adverse cardiac events, significantly lowered the interest in these drugs for heart disease (109,110), and TNF-α–blocking drugs are considered contraindicated in patients with or at risk of HF. Clinical studies targeting cytokines are summarized in Table 3.

Metalloproteinases. Metalloproteinases (MMPs) degrade collagen and can contribute to scar thinning and aneurysm formation and rupture in the infarcted area and to ventricular dilation and remodeling in remote areas (Fig. 2). Genetic blockade of MMP-2 (111) and MMP-9 (112) were shown to reduce cardiac rupture and improve ventricular remodeling after experimental AMI. PG-116800 is an oral MMP inhibitor with high affinity for MMP-2, -3, -8, -9, -13, and -14 and low affinity for MMP-1 and -7. In a phase II double-blind, multicenter RCT PREMIER (Prevention of Myocardial Infarction Early Remodeling) trial (113), PG-116800 given 2 days after STEMI to 203 patients with primary PCI and left ventricular ejection fraction 15% to 40% failed to improve ventricular remodeling at 6 months. Doxycycline, a tetracycline antibiotic, is also an MMP inhibitor that was shown to prevent ventricular remodeling after experimental AMI in rats through inhibition of MMP-2 and MMP-9 (114). In the phase II TIPTOP (Early Short-term Doxycycline Therapy In Patients with Acute Myocardial Infarction and Left Ventricular Dysfunction to Prevent The Ominous Progression to Adverse Remodeling) trial (115) (110 patients), treatment with doxycycline (100 mg twice daily) starting immediately after PCI and continued for 7 days was shown to reduce ventricular dilation at 6 months (increase in left ventricular end-systolic volume index: 0.4% vs. 13.4%, $p = 0.012$) and MACE (25.5% vs. 10.9%, $p = 0.04$) in patients with STEMI and left ventricular ejection fraction <40%. A phase II trial is enrolling patients with HF and nonischemic cardiomyopathy (116). Clinical studies targeting MMPs are summarized in Table 4.

Phosphoinositide 3-kinase. Phosphoinositide 3-kinase (PI3K) is a broad family of enzymes that phosphorylate phosphatidylinositol, participating in cell growth, proliferation, metabolism, migration, and inflammation in different cell types (117). LY294002, a broad PI3K inhibitor, showed no protective effect in ischemia-reperfusion (118). TG100-115, in contrast, is a selective PI3Kγ/PI3Kδ inhibitor that was shown to reduce infarct size after ischemia-reperfusion in mice and pigs through reduction of inflammation and edema (119). TG100-115 was tested in a phase I/II clinical trial in patients with STEMI in 2005, although results have not been published to date. Despite the proinflammatory effects of PI3Kγ in leukocytes, this isoform in cardiomyocytes contributes to normal contractility (120), independent of the kinase activity (121), likely related to a scaffold function modulating phosphodiesterase 3B. Genetic deletion of PI3Kγ led to adverse remodeling after AMI in mice (122), whereas pharmacological inhibition with AS605240 (123) or genetic removal of the kinase activity (122,124) showed improved or no effect on remodeling.

Immunoglobulin. Intravenous immunoglobulin (IVIG) is a pooled human immunoglobulin G antibodies from donors, with anti-inflammatory effects through several mechanism (121). In rats with AMI, IVIG treatment reduced inflammatory cytokines and MMP-2, although it did not affect survival or ventricular function at 7 days (125). A recent phase II RCT in 62 STEMI patients randomized to IVIG (0.4 mg/kg daily for 5 days, then monthly) or placebo showed no effect in ventricular remodeling at 6 months by cardiac magnetic resonance imaging (126).

Conclusions

Inflammation plays an important role in ventricular remodeling after AMI. Modulation of the inflammatory response represents a potential target for intervention. Despite early encouraging results in pre-clinical models with anti-inflammatory treatments, no beneficial effects on top of current medical treatments have been established in clinical studies. The number of strategies reported to be useful in the pre-clinical arena that have failed to show a benefit in clinical trials is disappointingly high due to many different and potentially overlapping reasons: 1) the use of rodents, which are significantly different from humans; 2) use of healthy and young animals that tend to exhibit an intense inflammatory response; 3) experimental AMI is performed via surgical ligation of a normal coronary artery, which differs substantially from the process of atherothrombosis; and 4) new therapies generally not tested in addition to current medical treatment.

The initial studies in patients with STEMI used broad inhibitors of inflammation that make it difficult to interpret results due to potential overlap of beneficial and deleterious effects. More recent studies in STEMI have aimed at single targets or signaling pathways and have provided some encouraging results that require validation. This parallels the approach of single cytokine or receptor targeting used in rheumatological and autoimmune disease. To date, no inflammatory inhibitor has been shown to conclusively improve outcomes beyond that with standard treatment.

From an evolutionary standpoint, the inflammatory/immune system appears to be a powerful adaptation to protect our species from the ubiquitous microbial flora, yet it is deleterious against noninfectious diseases, leading to both a chronic inflammatory response (as seen in atherosclerosis, diabetes, and obesity) and an exaggerated acute inflammatory response to tissue injury (as in AMI and stroke), mediating further injury. Indeed, there is solid evidence that inflammation plays a central pathological role in the progression of coronary atherosclerotic disease, AMI, and HF (127). However, more studies are needed to determine the most appropriate strategies to restore the inflammatory balance and ameliorate remodeling after AMI.

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